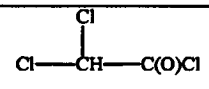
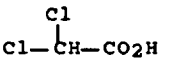
OVERALL SUMMARY FOR DICHLOROACETYL CHLORIDE

For the purposes of this document, dichloroacetyl chloride (also known as DCAC) data were searched and summarized. Data were also identified for the hydrolysis product, dichloroacetic acid (DCA). The available data for these chemicals is presented in Table 1. Each study on these materials was evaluated for adequacy. Robust summaries were developed for each study addressing specific SIDS endpoints. Summaries were also developed for studies either considered not adequate but that provided information of relevance for hazard identification and evaluation, or covered non-SIDS endpoints (Appendices A and B).

Table 1: Matrix of Available and Adequate Data

	Dichloroacetyl chloride (DCAC)	Dichloroacetic acid (DCA)
CAS Registry No.	79-36-7	79-43-6
STRUCTURE		
PHYSICAL/CHEMICAL CHARACTERISTICS		
Melting Point	N/A	√
Boiling Point	√	√
Density	√	√
Vapor Pressure	√	√
Partition Coefficient	√/-	√
Water Solubility	√	√
ENVIRONMENTAL FATE		
Photodegradation	√	√
Stability in Water	√	√
Transport (Fugacity)	√	√
Biodegradation	√	√
ECOTOXICITY		
Acute Toxicity to Fish	√*	√
Acute Toxicity to Invertebrates	√*	√
Acute Toxicity to Aquatic Plants	√*	√
MAMMALIAN TOXICITY		
Acute Toxicity	√	√
Repeated Dose Toxicity	√*	√
Developmental Toxicity	√*	√
Reproductive Toxicity	√*	√
GENETIC TOXICITY		
Genetic Toxicity Gene Mutations	√	√
Genetic Toxicity Chromosomal Aberrations	√*	√

√ = Data are available and considered adequate.
√/– = Data are available, but considered inadequate.
– = No data available.
N/A = Not Applicable.
√* = Data are available for an analog chemical (MCA) or hydrolysis product (DCA).

Physical and Chemical Characteristics

DCAC is a colorless liquid with an acrid, penetrating odor. DCAC hydrolyzes in water to form DCA and HCl. DCAC boils at 108°C, has a vapor pressure of 23 mm Hg @ 25°C, density of 1.53 @ 16/4°C, and a flash point of 66°C.

DCA is soluble in water. DCA has a melting point of 13.5°C, boiling point of 193-194°C, vapor pressure of 0.179 mm Hg @ 25°C, and density of 1.57 @ 13°C.

Data for physical and chemical characteristics are complete and no further testing is recommended.

Table 2: Physical and Chemical Characteristics

	DCAC	**DCA**
Melting Point	N/A	13.5°C
Boiling Point	108°C	193-194°C
Density	1.53 @ 16/4°C	1.57 @ 13°C
Vapor Pressure	23 mm Hg @ 25°C	0.179 mm Hg @ 25°C
Log Kow	-0.04 (estimated)	0.92 (measured)
Water Solubility	Hydrolyzes to DCA and HCl	> 100 g/L
Flash Point	66°C	No Data

Environmental Fate

Both dichloroacetyl chloride and dichloroacetic acid, the major organic hydrolysis product, will tend to exist in the vapor phase in the atmosphere, because they both have a vapor pressure greater than 0.01 mm Hg at 25^{o}C. Dichloroacetyl chloride that becomes vaporized and is not contacted by liquid water is subject to hydroxyl radical oxidation with an estimated half-life of 855 days. A half-life of 22 days is estimated for hydroxyl radical oxidation of vapor phase dichloroacetic acid. Dichloroacetyl chloride reacts rapidly upon contact with water (half-life substantially less than one second). The expected primary products from hydrolysis are dichloroacetic acid and hydrochloric acid (HCl). Environmental fate information for dichloroacetic acid indicates that it is soluble in water at > 100 g/L (SRC, n.d.). Dichloroacetic acid is estimated to have a Henry's Law constant of $3.52x10^{-7}$ atm-m^3/mole, which indicates that it has little tendency to volatilize from water. The estimated BCF value is 3, so it will not tend to bioaccumulate. It is reported to have an environmental half-life in temperate freshwater of < 100 hours (Ellis et al., 2001). The MITI database (CERI) reports that it is readily biodegradable, reaching 97% ThOD in 14 days. These characteristics indicate that dichloroacetyl chloride and its major degradation product, dichloroacetic acid, will not be persistent in water. Based on Level III fugacity modeling, using the assumption of equal emissions to air, water, and soil, any residual dichloroacetic acid is expected to be primarily distributed in water and soil. **No further environmental fate testing is recommended.**

Table 3: Environmental Fate

	DCAC	DCA
Bioaccumulation (BCF)*	Unstable in water	Low potential for bioaccumulation, BCF = 3
Biodegradation	Unstable in water	Readily biodegradable, 97% of ThBOD in 14 days (MITI test)
Fugacity*	Air 15.3% Water 49.5%[1] Soil 35.1% Sediment 0.096% Assuming equal emissions to air, water, and soil. [1] As implemented, the Level III model does not account for the rapid rate of hydrolysis. Such adjustments will tend to move the distribution away from water.	Air 4.05% Water 38.8% Soil 57.2% Sediment 0.077% Assuming equal emissions to air, water, and soil.
* Modeled data.		

Modeling of physical/chemical parameters (i.e., Kow) and aquatic toxicity was conducted to help provide insight into the behavior in the environment and the aquatic toxicity of DCAC. Syracuse Research Corporation models for estimating physical/chemical properties were used to estimate $\log_{10}$ Kow (Meylan and Howard, 1995) for subsequent use in the ECOSAR program (Table 4). ECOSAR (Meylan and Howard, 1999) was used to estimate the aquatic toxicity of DCAC to green algae, daphnids (planktonic freshwater crustaceans), and fish. ECOSAR predictions are based on actual toxicity test data for classes of compounds with similar modes of action. No empirical aquatic toxicity data exist for DCAC. It was not possible to use ECOSAR to estimate the aquatic toxicity of DCAC to either invertebrates or algae; however, it was possible to estimate the 96-hour LC_{50} for fish. It also was possible to use ECOSAR to estimate the acute toxicity of DCA (dichloroacetic acid) and its analog, MCA (monochloroacetic acid). Empirical data were also available for both of these compounds. Based on the available estimated or empirical data for DCA and MCA, the aquatic toxicity of DCAC is expected to be of low to medium concern. The toxicity of the other hydrolysis product of DCAC, hydrochloric acid, is likely to cause aquatic toxicity similar to or greater than DCA. Based on the rapid hydrolysis of DCAC and the availability of empirical data for its hydrolysis products, **no additional aquatic toxicity testing in recommended**.

Table 4: Aquatic Toxicity

	DCAC	**DCA**	**MCA**
Log Kow	-0.04 (E)*	0.52 (E)	0.34 (E)
Toxicity to Fish (96-hour LC_{50} value)	572 mg/L (E)	23,528 mg/L (E) 100 mg/L (24-hour LC_{50}, N)	25,457 mg/L (E) 370 mg/L (96-hour, M) LOEC = 25 mg/L (28-day, M)
Toxicity to Invertebrates (EC_{50} value)	No ECOSAR estimate	22,761 mg/L (48-hour, E) 23.0 mg/L (96-hour, N)	24,323 mg/L (48-hour, E) 96 mg/L (24-hour, N) 77 mg/L (48-hour, N) 32 mg/L (21-day NOEC, N)
Toxicity to Algae (96-hour EC_{50} value)	No ECOSAR estimate	13,067 mg/L (E) 29.8-264.3 mg/L (14-day endpoints, M)	13,820 mg/L (E) 0.028 mg/L (48-hour, N) 0.025 mg/L (72-hour, N) 1.8 mg/L (72-hour, N)
*E = estimated value, N = value based on nominal test concentrations, M = measured test concentrations			

Mammalian Toxicology

Acute toxicity data exists for both DCAC and its hydrolysis product, DCA. Both chemicals are slightly toxic via the acute oral route with LD_{50}s ranging from 2460 – 5520 mg/kg. Both chemicals are low to moderately toxic via the acute dermal route with LD_{50}s ranging from 0.51-650 mL/kg. Both DCAC and DCA are severe skin and eye irritants. **No further acute toxicity testing is recommended.**

Table 5: Acute Toxicity

	DCAC	DCA
Oral LD_{50}	2460 mg/kg (rat)	2820 - 4480 mg/kg (rat) 5520 mg/kg (mice)
4-hour Inhalation LC_{LO}	2000 ppm	No Data
Dermal LD_{50}	650 mL/kg	0.51 mL/kg
Dermal Irritation	Severe	Severe
Eye Irritation	Severe	Severe
Dermal Sensitization	No Data	No Data

Repeated Dose Toxicity

Repeated dose toxicity data exists for both DCAC and its hydrolysis product, DCA. DCAC produced nasal tumors in a repeated dose inhalation study. In repeated dose oral studies conducted with DCA, hematologic, liver, testicular, nervous system, and cardiovascular effects were observed.

In a 30-day repeated dose inhalation study in rats where rats were monitored post-exposure until they spontaneously died or were moribund, DCAC produced nasal tumors at 2 ppm. The NOEL for oncogenic effects was 1 ppm. DCAC was also tested for carcinogenicity in female mice by repeated skin application and repeated subcutaneous injection. DCAC did not show skin tumorigenicity in the repeated skin application tests when tested at dosages of 1.5 and 3.0 mg/administration. DCAC showed marginally significant incidences of papillomas and carcinomas when tested as an initiator (5/50 mice exhibited tumors). When tested via subcutaneous injection at 2.0 mg/administration, 4/50 mice exhibited tumors.

In a 3-month oral study, DCA produced mortality, hindlimb paralysis, and biochemistry effects in rats. Histopathology examinations revealed that brain and testes were the target organs. Brain lesions occurred mainly in the cerebrum and to a lesser extent in the cerebellum. DCA-treated males exhibited testicular germinal epithelial degeneration and aspermatogenic testes. The LOAEL in rats was 125 mg/kg (the lowest dose tested). In dogs, DCA produced mortality, paralysis, biochemistry effects, and a high incidence of ocular anomalies. Histopathology findings included the ocular lesions, as well as effects in the lungs, brain, prostate, and testes. The LOAEL in dogs was 50 mg/kg (the lowest dose tested). A NOAEL was not established in rats or dogs.

In another 90-day oral study in dogs, DCA produced mortality, bilateral conjunctivitis, posterior paresis, and biochemical effects. The microscopic exam revealed effects in the brain, liver, lung, pancreas, and testes. A NOAEL was not determined in this study. The LOAEL was 12.5 mg/kg.

In an oral drinking water carcinogenicity study in rats, DCA induced observable signs of toxicity in the nervous system, liver, and myocardium. However, treatment-related neoplastic lesions were observed only in the liver. Testicular interstitial cell tumors were seen. DCA was considered a hepatocellular carcinogen in the male F344 rat. The authors state a NOEL of 0.05 g/L for DCA carcinogenicity in this study. **No further repeated dose toxicity testing is recommended.**

Table 6: Repeated Dose Toxicity

	DCAC	**DCA**
Repeated Dose Studies	30-Day Inhalation Study: Nasal tumors at 2 ppm. NOEL = 1 ppm (rats)	3-Month Oral Study: Peripheral neuropathy, brain, ocular, prostate, liver, lung, pancreas, and/or testes effects LOAEL = 125 mg/kg (rats) and 12.5 mg/kg (dogs). NOAELs were not determined.
Oncogenicity Study	Skin tumors at 3.0 mg/administration in a dermal initiation/promotion assay. NOEL not determined (mice).	Neoplastic lesions in the liver. NOEL = 0.05 g/L (rats)

Developmental Toxicity

No developmental toxicity data were available for DCAC. DCA was administered to rats during gestation days 6-15 at dosages of 0, 14, 140, 400, 900, 1400, 1900, and 2400 mg/kg. Maternal toxicity as evidenced by reduced body weight gains was observed at = 140 mg/kg. Maternal death was observed at = 1400 mg/kg. Lower fetal weight and length and increased soft tissue malformations (cardiovascular system and ascending aorta and right ventricle) were observed at = 140 mg/kg. Since the NOEL for both maternal and fetal effects was 14 mg/kg/day, DCA was not considered a unique developmental toxin. **No further developmental toxicity testing is recommended.**

Reproductive Toxicity

While no formal reproductive toxicity studies have been conducted on DCAC, pathological examination of the testes in the 30-day inhalation study did not reveal any compound-related effects. A 14-day oral gavage study of DCA in rats, on the other hand, revealed delayed spermiation, formation of atypical residual bodies, distorted sperm heads and acrosomes, decreases in percentage of motile sperm, increased numbers of fused epidiymal sperm, and decreased epididymal weight and sperm count. No effects on the sperm were observed at

18 mg/kg. Testicular effects were also apparent in the repeated dose tests described earlier. Testicular degenerative lesions were observed as low as 12.5 mg/kg in a 90-day oral study in dogs. **No reproductive toxicity testing is recommended.**

Genetic Toxicity

DCAC was positive in a microscreen prophage induction assay. DCAC was also positive in a bacterial reverse mutation assay using *Salmonella* TA100 when tested without metabolic activation, but was negative in TA100 with metabolic activation. Molecular analysis of *Salmonella* revertants indicated that DCAC primarily induced GC to AT transitions. In a second bacterial reverse mutation assay using *Salmonella* TA98 and TA100, DCAC was again positive without metabolic activation in TA100, but was negative with metabolic activation in TA100 and TA98, and negative without metabolic activation in TA98. No data on the clastogenicity of DCAC were available.

DCA was also positive in a microscreen prophage induction assay. Both negative and positive results have been observed in bacterial mutation assays in *Salmonella* and *E. coli.* DCA was negative without metabolic activation and positive with activation in a DNA repair test, negative and positive in mouse lymphoma tests, positive in a cytogenetics test, negative in an *in vitro* micronucleus test, and negative in a CHO test. When tested *in vivo*, DCA was positive and negative in micronucleus tests, positive for mutagenicity in mouse liver, negative in an 8-OH DNA adduct test, and positive in a DNA strand breaking test. **No genetic toxicity testing is recommended.**

Table 7: GeneticToxicity

	DCAC	**DCA**
Mutagenicity	Mutagenic	Mutagenic
Clastogenicity	No Data	Clastogenic

Conclusion

Adequate data are available to address all the required endpoints. A substantial body of data exists for DCAC *per se*. Where data are lacking on DCAC, reliable data are available for the hydrolysis product, DCA. The use of DCA data to supplement the existing mammalian toxicity data for DCAC is supported by the close similarity in molecular structure, similarity in physical/chemical properties, and the similarity in toxicity observed where data for both substances are available for comparison. DCAC is rapidly hydrolyzed in aqueous media (half-life in water is <0.22 seconds) to DCA and HCl. The use of DCA data for DCAC is consistent with the Agency's directive to HPV participants to maximize the use of scientifically appropriate data for related chemicals. Although some differences between DCA and DCAC may be expected, we believe these differences to be minimal and insufficient to warrant additional animal testing.

Justification for Isolated Intermediate Status[1]:

DCAC is manufactured at Mobile and shipped to a small number of customers. Transportation is by tank truck or ISO, which are dedicated to DCAC service. The manufacturing process is a closed system, dedicated to DCAC manufacture. The shipping containers are closed with vent gases sent to a scrubber. Overfill protection for the loading operation is provided by a mass meter and there is spill containment at the rail spot including catch pan and sump. Any spills are treated in on-site waste facilities. For operations involving potential for DCAC exposure (line breaks, sampling, loading and unloading) proper PPE includes use of a butyl suit and full-face respirator with an airline supply. A full-face mask with acid cartridge would also be acceptable. Fresh cartridges each time are recommended to avoid break-through.

The customers who receive DCAC use it as a chemical intermediate in synthesis of other products. Their manufacturing systems are closed. Spill containment is used at the unloading spots, and PPE worn to protect the operators. Stewardship reviews of the customer facilities are conducted by DuPont personnel to verify the standards and practices are maintained.

References for the Summary:

Ellis, D. A. et al. (2001). Chemosphere, 42(3):309-318.

Meylan, W. M. and P. H. Howard (1995). J. Pharm. Sci., 84:83-92.

Meylan, W. M. and P. H. Howard (1999). User's Guide for the ECOSAR Class Program, Version 0.993 (Mar 99), prepared for J. Vincent Nabholz and Gordon Cas, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, DC, prepared by Syracuse Research Corp., Environmental Science Center, Syracuse, NY 13210.

SRC (Syracuse Research Corporation) (n.d.). (HSDB/6894).

[1] As defined by EPA guidance, an isolated intermediate is one in which there is controlled transport, i.e. to a limited number of locations within the same company or second parties that use the chemical in a controlled way as an intermediate with a well known technology.